REMARKS

This paper is responsive to the Office Action dated March 27, 2007, which is the first Action on the merits of the application.

Claims 32-45 were previously pending in the application. Certain claims have been amended in this response, and claim 38 has been cancelled. New claims 46-54 have been added, and fall into the group under examination. Accordingly, claims 32-37 and 39-54 are now pending in the application, with claims 32-37, 39-43, and 46-54 under examination.

Further consideration and allowance of the application is respectfully requested.

Claim amendments:

The priority information in paragraph 1 of the specification is amended herein in response to the Examiner's request.

The amendments to the claims do not introduce new matter into the disclosure. Support for the amended and the new claims may be found at various places in the specification. Citations below are made to the application as published (US 2004/0116372 A1).

Claim 32:	Paragraphs [0059] and [0074]
Claim 41 & 42:	Paragraphs [0027] and [0034]
Claims 46 & 52:	Paragraph [0065]
Claims 47 & 51:	Paragraph [0059] (line 1 on page 6, col. 1)
Claims 48 & 54:	Paragraphs [0009], [0023], and [0031]
Claim 49:	Paragraph [0031]
Claim 50:	Paragraphs [0023] and [0026]; Fig. 5
Claim 53:	Paragraphs [0028] and [0058]

Restriction:

Applicants are grateful that the Examination has examined the product claims in the Office Action, as requested in applicants' response to the previous restriction requirement. With respect to the species elections, applicants respectfully submit that the p53 polypeptide of claim 39, and the p53 peptidomimetic or binding agent of claim 40 can be searched simultaneously without undue burden on the Examiner, and thus claim 40 should be incorporated into the group under examination.

Applicants note that previously presented claims 31-45 have been divided in this Office Action into separately patentable inventions: namely, the product of claims 31-43, and the methods of claims 44-45. Although the method claims depend from and incorporate limitations from the product claims, applicants hereby request that *claims 44-45 not be rejoined into the group under examination, unless explicitly requested.*

Drawings and Information Disclosure Statement:

The Office Action indicates that Figure 1 does not meet the draftsperson's requirements. Enclosed herewith is a replacement figure. Please enter this into the application in place of Figure 1 of the application as filed. No amendment has been made to the figure beyond what was undertaken to bring the figure into compliance with 37 CFR § 1.121(d).

The Office Action also indicates that the PTO-1449 accompanying the Information Disclosure Statement filed November 18, 2003 is not in compliance with the requirements. A new PTO-1449 is enclosed herewith.

Following under separate cover is a new IDS incorporating published patent application US 2007/0065421 A1, and additional publications from scholarly journals.

The Examiner is respectfully requested to make all references in both IDSes of record in the application.

Just one fee under 37 CFR § 1.117(p) is believed necessary for consideration of both these IDSes at this stage of examination. The fee is enclosed herewith.

Rejections under 35 USC § 102:

The claims under examination stand rejected under 35 USC §102(e) as being anticipated by U.S. Patent 5,747,463 (the "Roth patent"). The Office Action indicates that the Roth patent teaches a nucleic acid encoding wild-type p53 operably linked to a constitutive promoter, formulated in a pharmaceutical composition for administration to a subject. The Office Action also indicates that the previous wording in the claim referring to the composition as being "formulated for administration to an arthritic or inflamed joint" is not considered to constrain the claimed subject matter, since it appears in the preamble.

Claim 32 has now been amended to place the feature of being *formulated for administration to an arthritis or inflamed joint* more clearly as a claim limitation. A second feature that is now required is that the composition is *formulated for transfection of synoviocytes* within said joint. A third feature that is now required is that the a*mount of the vector in the composition is therapeutically effective for reducing signs of arthritis or inflammation* upon administration into a joint of a mammalian subject.

Applicants respectfully submit that these features distinguish the products claimed in the present application from anything taught in the Roth patent.

In making this rejection, the Office presumes that the p53 nucleic acid compositions described by Roth et al. would *inherently* have all the requirements of the invention claimed here. The Roth patent describes compositions for killing *tumor* cells by *direct injection,* possibly in combination with a DNA damaging agent (claim 1). In contrast, claim 32 of this application as amended herein explicitly requires that the composition be formulated for injection into joints, for transfecting synoviocytes, and for effectively treating an inflammatory or arthritic condition.

To make a rejection based on inherency, the law requires that the prior art composition must *necessarily* contain all the limitations of the subject invention[1]. Applicants respectfully submit that the rejection as presented in the Office Action does not establish a prima facie case for rejection of the claimed invention in view of inherent properties of the compositions in the Roth patent.

Furthermore, even if a prima facie case for inherency in the prior art is made, applicants can overcome a rejection by showing that the prior art product does not necessarily possess the characteristics of the claimed invention[2]. In this regard, applicants submit that subsequent publications by the same group show that the p53 constructs described in the Roth patent would not be expected to work for the treatment of arthritis.

Enclosed with this response is an article by Clayman, Roth et al., Cancer Res. 55:1-6, 1995. On page 3, the article states the following:

> [W]e investigated the effect of the Ad5CMV-p53 on karyotypically normal and nontumorigenic fibroblast cell lines. These cells were isolated during the establishment of primary tumor cell lines. Twenty four h after infection, Western blot analysis was performed to compare the levels of protein produced by the different infected cell types. A p53 band, recognized by the monospecific anti-p53 antibody, PAblSOl, was observed in cellular extracts isolated from all samples infected with the Ad5CMV-p53 (Fig. 2A; Lanes 1 and 4). As has been shown previously [Liu et al., Cancer Res. 54:3662-3667, 1994], cell line Tu-138 infected with the p53 adenovirus showed high levels of p53 protein following

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1 The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert,* 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " I*n re Robertson,* 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted).

2 [T]he prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. *In re Best,* 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977).

> transduction and served as a control (Fig. 2A; Lane 1). The level of p53 expression remained similar in both mock-infected and dl312-infected cells (Fig. 2A; Lanes 2 and 3). The Ad5CMV-p53-infected fibroblasts showed higher levels of p53 protein than did the control cells (Fig. 2A; Lane 4). This result indicates that the p53 gene is efficiently translated into normal fibroblasts infected with Ad5CMV-p53 as evidenced by production of immunoreactive p53 protein. The protein expression and transduction efficiency of cytospins of Ad5CMV-p53 infected fibroblasts were verified by immunohistochemical analysis (data not shown). This fibroblast cell line exhibited normal growth rate and morphology independent of the intervention (mock, replication-defective virus, or Ad5CMV-p53) (Fig. 2B). These experiments were repeated twice and also verified in other normal human fibroblast cell lines.

Thus, the p53 vector used by Clayman and Roth *failed* to impair the growth of human fibroblasts isolated from the same tissue sample as susceptible tumor cell lines — and also failed to impair the growth of other human fibroblast cell lines.

Evidently, the product described in the Roth patent was not suitably formulated for transfecting fibroblasts, and/or the dose used was inadequate. Applicants do not mean to suggest that optimizing of formulation and dosage of a p53 vector for treating arthritis in a joint would be a difficult process. But the prior art product clearly fails to meet the limitations of the claim, and there is no motivation for someone reading the Roth patent to reformulate the vector for this purpose, since it is clearly effective in its intended purpose of killing tumor cells[3].

Withdrawal of this rejection is respectfully requested.

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[3] Shown *inter alia* in Examples 5 and 6 of the Roth patent (Cols. 26-30). The underlying theory of the invention claimed in the present action is different: the purpose of the p53 vector is not to initiate a new apoptotic pathway in cancer cells, but to *restore* an existing apoptotic pathway that has become defective in fibroblast-like synoviocytes — a pathway which is normally active to keep cells from accumulating in the joint and causing tissue damage. This is explained in the present application in the Summary (paragraph [0008]) and in the detailed description (paragraph [0023]). Since the two inventions are directed at two different tissue types for different underlying reasons, it cannot reasonably be presumed that the dosing and formulation would be identical.

Request for Interview

Applicant respectfully requests that the rejection under 35 USC §102 be reconsidered and withdrawn, and that the other species of apoptosis genes (claim 39) and inflammatory conditions (claim 42) be rejoined into the group under examination. The application is believed to be in condition for allowance, and a prompt Notice of Allowance is requested.

In the event that the Examiner determines that there are other matters to be addressed, applicant hereby requests an interview by telephone.

Conclusion

Applicants submit that pending claims 32-37, 39-43, and 46-54 are in condition for allowance. The Examiner is invited to contact Applicants' undersigned representative if there are any questions relating to this submission.

Enclosed with this Amendment is the fee required for the Information Disclosure Statements and for the claim amendments. No other fee is believed to be due in connection with filing this paper. However, the Commissioner is hereby authorized to charge any other fees associated with the filing submitted herewith, or credit any overpayments to Deposit Account No. 07-1896 referencing the above-identified attorney docket number. A copy of the Transmittal sheet is enclosed.

Respectfully submitted,

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Daryl A. Basham, J.D., Ph.D.
Registration No. 45,869
Telephone: (858) 677-1429
Facsimile: (858) 677-1465

DLA PIPER US LLP
4365 Executive Drive, Suite 1100
San Diego, California 92121-2133
USPTO Customer Number 28213

Enclosures